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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/750,410	12/28/2000	Gloria C. Li	55672-A-PCT-US/ JPW/AJM/M	6916

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 11/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/750,410	LI ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 December 2000*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-26 are pending in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16-18, 25 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "substance which inactivates mRNA" in claim 16, line 2, is vague and unclear. Appropriate clarification is requested.

The phrase "linked to a regulatory subunit" in claim 18, lines 1 and 2, is vague and unclear. Appropriate clarification is requested.

The phrase "adapted for passage through a plasma cell membrane" in claims 25 and 26, lines 2 and 3, is vague and unclear. Appropriate clarification is requested.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to compositions and methods comprising the administration of antisense oligonucleotides that specifically hybridize to a nucleic acid encoding a DNA dependent protein kinase catalytic subunit, or a Ku 70 or a Ku 80 subunit, and which antisense are optionally linked to a regulatory element. The claims are also drawn to antisense oligonucleotides that are linked to a substance which inactivates mRNA, and are drawn to pharmaceutical compositions comprising a carrier adapted for passage through a plasma cell membrane. The specification and claims do not describe the elements that are essential to the broad genus comprising nucleic acids encoding any DNA dependent protein kinase catalytic subunit , or any Ku 70 or any Ku 80 subunit, or antisense optionally linked to any regulatory element. The specification and claims do not disclose the elements that adequately describe the broad genus comprising any substance which inactivates mRNA, or any carrier adapted for passage through a plasma cell membrane. The specification and claims do not indicate what distinguishing attributes are concisely shared by members of the each of these broad genera, comprising nucleic acids encoding any DNA dependent protein kinase catalytic subunit, or any Ku 70 or any Ku 80 subunit, or antisense optionally linked to any regulatory element, or substances which inactivate mRNA, or pharmaceutical compositions comprising a carrier adapted for passage through a plasma cell membrane. The scope of the claims includes numerous structural variants, and each genus is highly variant because a significant number of structural differences between members of a given genus is permitted. Concise structural features that could

distinguish structures or compounds within a genus from others are missing from the disclosure. No common structural attributes identify the members of each genus. The general knowledge and level of skill in the art do not supplement the omitted descriptions because specific, not general guidance is what is needed. The specification fails to teach or adequately describe a representative number of species in each genus such that the common attributes or characteristics concisely identifying members of each proposed genus are exemplified. And because each genus is highly variant, the description provided is insufficient. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the various genera claimed. Thus, Applicant was not in possession of the broadly claimed genera.

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions and methods for increasing the susceptibility of a cell to DNA-damaging agents comprising the in vitro administration of an antisense oligonucleotide that specifically hybridizes to and inhibits the expression of a nucleic acid encoding a subunit of mouse or human DNA dependent protein kinase, does not reasonably provide enablement for increasing the susceptibility of a cell to DNA-damaging agents in vivo, or to treat any tumor or any cancer in a subject, comprising the administration of an antisense oligonucleotide that specifically targets and inhibits the expression of any nucleic acid encoding any subunit of DNA dependent protein kinase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The claims are drawn to methods of increasing the susceptibility of a cell to DNA-damaging agents in vivo or in vitro, or to treat any tumor or any cancer in a subject, comprising the administration of an antisense oligonucleotide that specifically targets and inhibits the expression of nucleic acids encoding any subunit of any DNA dependent protein kinase.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of antisense treatment in organisms. Branch and Crooke teach that the in vivo (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of *in vivo* inhibition of target genes. (See entire text for Branch and especially pages 34-36 for Crooke). The high level of unpredictability regarding the prediction of antisense efficacy in treating disease states was illustrated in the clinical trial results obtained by ISIS pharmaceuticals for the treatment of Crohn's disease using antisense targeting ICAM-1, whereby the placebo treatment was found more successful than antisense treatment (BioWorld Today: See entire article, especially paragraphs 3 and 5-7 on page 1). Additionally, Palu et al teach that the success of gene delivery using virally derived vectors is dependent on the empirical determination of successful gene transduction for a given vector and a given target cell (See entire article, especially page 4, section 2).

Tamm et al, in a review article discussing the therapeutic potential of antisense in treating various forms of neoplasia, conclude that "Proof of clinical efficacy, of any of the antisense oligonucleotides in the field of oncology, is still missing." (see especially pages 490-493 for a summary of various clinical trials in process using antisense). Additionally, Agrawal et al point to various factors contributing to the unpredictability of antisense therapy, including non-antisense effects attributed to secondary structure and charge, as well as biological effects exerted by sequence motifs existing within the antisense sequences, all providing for unpredictable in vivo side effects and limited efficacy (e.g. see pages 72-76). Agrawal et al speak to the unpredictable nature of the antisense field thus: "It is therefore appropriate to study each antisense oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide." (see page 80).

Cellular uptake of antisense oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using antisense. Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of antisense oligonucleotides in vitro and in vivo (see Agrawal et al especially at pages 79-80; see Chirila et al in its entirety, especially pages 326-327 for a general review of the "important and inordinately difficult challenge" of the delivery of therapeutic antisense oligonucleotides to target cells).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of increasing the susceptibility of a cell to DNA-

damaging agents in vivo or in vitro, or to treat any tumor or any cancer in a subject, comprising the administration of an antisense oligonucleotide that specifically targets and inhibits the expression of nucleic acids encoding any subunit of DNA dependent protein kinase. (DNA PK), in vitro or in vivo.

The specification teaches the germline disruption of Ku70 and Ku80 in mouse models. The specification also teaches the targeted disruption of the catalytic subunit of DNA PK in a mouse model. The specification fails to teach the increase in susceptibility of a cell to DNA-damaging agents, or treatment of tumors or cancer in any organism, comprising the administration of antisense targeting any nucleic acid encoding any subunit of DNA PK. One skilled in the art would not accept on its face the examples given in the specification of the germline disruption of Ku70 and Ku80, or the targeted disruption of the catalytic subunit of DNA PK as being correlative or representative of the increase in susceptibility of a cell to DNA-damaging agents, or the treatment of tumors or cancer in any organism comprising the administration of antisense, in view of the lack of guidance in the specification and known unpredictability associated with the ability to predict the in vivo effects of antisense in treating any cancer or tumor in an organism, or increasing the sensitivity of cells in vivo comprising the administration of antisense. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with in vivo delivery and treatment effects provided by antisense administered, and specifically regarding the instant compositions and methods claimed.

The breadth of the claims and the quantity of experimentation required.

The breadth of the claims is very broad. The claims are drawn to methods of increasing the susceptibility of a cell to DNA-damaging agents in vivo or in vitro, or to treat any tumor or any cancer in a subject, comprising the administration of an antisense oligonucleotide that specifically targets and inhibits the expression of nucleic acids encoding any subunit of any DNA dependent protein kinase. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues harboring the target gene DNA dependent protein kinase, whereby any subunit of any DNA dependent protein kinase expression is inhibited in vitro and in vivo, and further whereby increased DNA damage occurs to target cells in vitro or in vivo, or treatment effects are provided for any tumors or cancers in an organism. Since the specification fails to provide any particular guidance for the successful inhibition of expression of any DNA dependent protein kinase subunit in vitro or in vivo comprising the administration of antisense, and fails to provide guidance for the successful treatment of tumors or cancers in an organism comprising the administration of antisense, and since determination of these factors is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

Claim Rejections - 35 USC § 102

person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claim 15 is rejected under 35 U.S.C. 102(e) as being anticipated by Hasty et al ((USPN 5,955,644)

Hasty et al teach antisense oligonucleotides specifically targeting a nucleic acid encoding a DNA dependent protein kinase subunit, which antisense inhibit the expression of the target DNA PK in vitro, and increase its sensitivity to DNA-damaging agents (See col. 2, line 4 - col. 4, line 17; col. 4, line 67 – col. 5, line 17; col. 9, line 57 – col. 10, line 42; col. 13, lines 12-23).

Claims 15, 23, 25 and 26 are rejected under 35 U.S.C. 102(e) as being anticipated by Housman et al (USPN 6,200,754).

Housman et al teach pharmaceutical compositions comprising antisense oligonucleotides specifically targeting a nucleic acid encoding a DNA dependent protein kinase subunit, which antisense inhibit the expression of the target DNA PK in vitro, and

increase its sensitivity to DNA-damaging agents, and which compositions further comprise liposomes for intracellular delivery of antisense (See col. 12, line 49-col. 15, line 54; col. 27, lines 13-25; col. 28-29; col. 42, line 46 – col. 44, line 11; and claims 3, 10 and 11).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 15, 18-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Housman et al as applied to claims 15, 23 above, and further in view of Chiorini et al.

The claims are drawn to pharmaceutical compositions comprising antisense oligonucleotides specifically targeting a nucleic acid encoding a DNA dependent protein kinase subunit, which antisense inhibit the expression of the target DNA PK, and which

antisense is operably linked in an appropriate expression vector to a heat shock promoter.

Housman et al teach pharmaceutical compositions comprising antisense oligonucleotides specifically targeting a nucleic acid encoding a DNA dependent protein kinase subunit, which antisense inhibit the expression of the target DNA PK in vitro, and increase its sensitivity to DNA-damaging agents, and which compositions further comprise liposomes for intracellular delivery of antisense (See col. 12, line 49-col. 15, line 54; col. 27, lines 13-25; col. 28-29; col. 42, line 46 – col. 44, line 11; and claims 3, 10 and 11).

Housman et al do not teach antisense oligonucleotides operably linked in an appropriate expression vector to a heat shock promoter.

Chiorini et al (USPN 5,693,531) teach antisense oligonucleotides operably linked in an appropriate expression vector to a heat shock promoter (See col. 3, lines 4-32).

It would have been obvious to one of ordinary skill in the art to insert antisense oligonucleotides into an appropriate expression vector, operably linked to an inducible promoter including a heat shock promoter, because such expression systems have been used routinely in the art for expression of operably linked nucleic acid constructs in an appropriate target cell, as taught previously by Chiorini et al. One of ordinary skill in the art would have been motivated to operably link an antisense oligonucleotide to an inducible promoter in an appropriate expression vector in order to control the conditions of expression of the operably linked antisense, and in order to control antisense expression and subsequent inhibition of the antisense's target gene. One of ordinary

skill in the art would have expected that by utilizing appropriate conditions for induction that the antisense would be expressed upon induction of the heat shock promoter because the heat shock promoter has been described by Chiorini et al and this technique of inducible expression of operably linked nucleotides was well known in the art at the time the invention was made. Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER

JZ
November 16, 2003